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Omitting Cardiophrenic Lymph Nodes in the Treatment of Patients with Hodgkin Lymphoma via Modified Involved-Site Radiation Therapy

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Abstract

Cardiophrenic lymph node (CPLNs) are occasionally involved in Hodgkin Lymphoma (HL). We characterized the incidence of CPLN involvement among 169 HL patients and evaluated outcomes after treatment with omission of the CPLN region from the Involved Site Radiation Therapy (ISRT) field. Three types of RT fields were used: standard (S)-ISRT, reduced-dose (RD)-ISRT (lower dose to CPLNs, standard to other sites), or modified (M)-ISRT (omission of CPLNs). CPLNs were involved at diagnosis in 29 patients (17%). Of the 20 patients who received RT after complete response to chemotherapy, 4(20%) received S-ISRT, 8(40%) RD-ISRT, and 8(40%) M-ISRT. The 4-year progression-free survival was 94.7%. One relapse occurred at a non-CPLN site after RD-ISRT. The mean heart dose and volume of the heart that received 25 Gy was higher for S-ISRT patients compared to M-ISRT ($P=0.043$ and $P=0.025$, respectively). Re-planning the M-ISRT cases for S-ISRT resulted in significant increase in cardiac doses.

Keywords

Hodgkin Lymphoma; Radiation Therapy; Cardiophrenic Lymph Nodes

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INTRODUCTION

A current standard therapy for stage I and II Hodgkin lymphoma (HL) is doxorubicin-based chemotherapy followed by consolidative involved-site radiation therapy (ISRT) to initial sites of disease [1]. Although this approach produces excellent cure rates, concerns remain regarding long-term toxicity. Patients with supra-diaphragmatic HL treated with RT are at the highest risk for cardiac late effects and secondary malignancies, which correlate strongly with the radiation doses and volumes administered [2,3].

Consolidative RT is associated with improved progression-free survival (PFS), even after a complete response to chemotherapy [4,5]. Efforts have been made to maintain the benefit provided by RT while minimizing the associated toxicity by reducing the irradiated volume. The current standard of care, ISRT, targets initial sites of disease with only small margins for set-up variation [1]. Although the smaller RT target volumes reduce the dose to organs at risk (OARs) relative to traditional involved fields, in some cases RT fields can still be large owing to the initial disease distribution. This has led some clinicians to omit RT because of concerns regarding late toxicity.

Supra-diaphragmatic HL most often affects the central mediastinal nodes namely; anterior mediastinal, paratracheal, subcarinal, and hilar nodal groups [6]. Lymph nodes along the diaphragm adjacent to the inferior aspect of the heart, or cardiophrenic lymph nodes (CPLNs), are a less common but established pattern of disease involvement [7–9]. In the modern-day ISRT era, even conformal RT approaches such as proton therapy or intensity-modulated radiation therapy (IMRT) that include CPLNs tend to increase cardiac, pulmonary, and, for female patients, breast radiation exposure. In cases where RT doses to surrounding normal organs may be exceeded, ISRT target volumes may be modified to minimize toxicity [1].

Our current approach for patients with involved CPLNs is individualized. When including CPLNs within a standard ISRT (S-ISRT) field would result in unacceptably high doses to OARs, we either treat this region to a lower dose (reduced-dose [RD] -ISRT) or exclude the CPLN areas from the field entirely (modified [M] -ISRT). The aim of the current study was to characterize the incidence of CPLN involvement among HL patients and the clinical and dosimetric effects of S-ISRT, RD-ISRT or M-ISRT for patients with HL and CPLN involvement. We compared doses to OARs for each approach, and we generated S-ISRT comparison plans for patients who received M-ISRT to determine the dosimetric effect of S-ISRT on OARs.

METHODS AND MATERIALS

After approval by our institutional review board, we examined the electronic medical records of patients who received RT for HL from January 2009 through December 2015 at MD Anderson Cancer Center. Clinical notes, radiographic examinations, and RT records were reviewed. Most patients had received 4–6 cycles of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD). All baseline ^{18}F -fluorodeoxyglucose positron emission tomography-computed tomography (PET-CT) studies were reviewed for baseline CPLN involvement.

Boundaries of the cardiophrenic region were along the anterior diaphragm adjacent to the inferior aspect of the heart in an arc, extending on the right from the inferior vena cava to the phrenic nerve on the left [9]. Bulky mediastinal masses that extended contiguously to the cardiophrenic region were not considered CPLN involvement, but discontinuous PET-CT-avid nodal masses in this region were. Involvement was confirmed by a nuclear medicine. The maximum axial dimension of the CPLNs was determined on the baseline PET-CT images. A second set of PET-CT images was obtained after first-line chemotherapy but before RT. Responses were assessed on the 5-point Deauville scale [10], with a Deauville score of 1–3 considered a complete response (CR) to therapy. End-of-chemotherapy PET-CT images were evaluated for the presence of CPLN remnants, defined as any nodal or soft tissue mass in the previously involved CPLN site. If such a remnant was identified, its maximum size in the axial plane was recorded.

The Kaplan-Meier method was used to estimate PFS, defined as the interval between the date of diagnosis and the date of relapse, disease progression, or death from any cause and was censored at the time of last follow-up.

Radiation Therapy

External-beam RT was given as consolidative therapy to a dose of 30.6 Gy in 17 fractions after a CR to chemotherapy. IMRT was used in all cases, often with an anterior-posterior weighted “butterfly” beam arrangement with 6-MV coplanar photons [11]. Most female patients were treated on a 15° inclined board to reduce the breast dose. For patients treated after 2012, the deep inspiration breath-hold (DIBH) technique was used. If DIBH was not used, four-dimensional CT scans were used to account for respiration-induced target motion. Daily kV imaging or low-dose CT-on-rails (Varian Medical Systems, Palo Alto, CA) was used for image-guided therapy. Since staging PET-CT imaging is not performed with breathhold, when RT was delivered to the CPLN region with DIBH technique, daily CT on rails imaging coupled with adequate PTV margin was essential for accurate RT delivery. For patients treated with S-ISRT, the clinical target volume (CTV) included sites of involvement identified on baseline (pre-chemotherapy) PET-CT image, as described by the International Lymphoma Radiation Oncology Group (ILROG) [1]. We began routinely using standard ISRT in 2008, before the guidelines were published. The planning target volume (PTV) margin was generally 5–10 mm and was based on daily imaging. For patients treated with RD-ISRT, all sites of initial involvement were treated to a dose of 30.6 Gy except for CPLN sites, which were limited to 19.8–25.2 Gy. Treating physicians tended to use RD-ISRT when there was concern for exceeding normal tissue constraints with standard ISRT coupled with reluctance to completely omit the CPLN site from the target volume based on perceived risk of relapse (often in cases of larger CPLNs or significant residual masses). For patients treated with M-ISRT, CPLN sites were excluded from the CTV.

Organ-At-Risk Delineation and Dosimetric Analysis

All treatment plans were stored in a Pinnacle planning system (Phillips Radiation Oncology Systems, Fitchburg, WI). The OARs contoured were the total heart, left ventricle (LV), left main/left anterior descending (LAD) artery, right coronary artery, total lung, and (in female patients) bilateral breasts. The heart and its substructures were contoured according to a

validated heart atlas [12]. The total lung contour consisted of the bilateral lungs as seen on the planning CT scan and included lung tissue within the CTV and PTV. The bilateral breast contours included all visible glandular mammary tissue on the planning CT scan.

Dosimetric and Comparison Plan Analysis

The mean dose and the volumes receiving 25 Gy (V25) and 5 Gy (V5) were collected for the heart, LV, left main/LAD, right coronary, and bilateral breasts. Mean heart dose has been correlated with long term cardiac toxicity [13,14]. LV V25 has been linked with subsequent cardiac perfusion defects [15]. For the lung, the mean dose, V20, and V5 were collected based on published associations between these variables and radiation pneumonitis among patients with lymphoma treated with IMRT [16]. The mean of each dosimetric variable was determined for each treatment group. Groups were compared using one-way analysis of variance (ANOVA) tests, with homogeneity of variance confirmed prior to use of ANOVA (Levene's test statistic was calculated for each ANOVA, and $P > 0.05$ for all tests of homogeneity unless specified otherwise). Post-hoc least significant differences (LSD) tests were implemented after ANOVA to assess pairwise comparisons between groups. For cases where $P > 0.05$ using the Levene's statistic, independent-samples Kruskal-Wallis tests were utilized for comparison of group medians.

For the 8 patients who received M-ISRT (i.e., one or more CPLNs excluded), a second comparison plan was generated by a certified dosimetrist or medical physicist. That plan encompassed all initial disease sites, including the involved CLPNs, according to ISRT guidelines. Paired two-sided t tests were used to assess potential differences in doses to OARs ($P > 0.05$) between the sets of plans. Homogeneity of variance using the Levene's statistic was confirmed for all t tests, with $P > 0.05$ for all paired t tests in this study.

RESULTS

We identified 169 consecutive patients who had received RT for HL from 2009 through 2015 (Table 1). Cardiophrenic involvement was present in 29 patients (17%). Of those 29 patients, 69% were female and 90% had Ann Arbor stage II disease; 16 patients (55%) had bulky mediastinal involvement (disease > 10 cm in axial dimension on CT). The median number of CPLNs was 1 (range 1–8), and the median size of the largest node was 2.2 cm (range 0.9–10.1 cm). Twenty of the 29 patients with initial CPLN involvement received RT after a CR to chemotherapy (i.e., in first remission), and 9 had RT for relapsed or refractory disease. The 9 patients with initial CPLN involvement that eventually received RT for relapsed or refractory disease received salvage chemotherapy with (n=7) or without (n=2) autologous stem cell transplantation followed by consolidative RT.

To evaluate outcomes after M-ISRT, we analyzed the 20 patients given RT after a CR to chemotherapy (Table 2). All patients had received 4–6 cycles of doxorubicin, vinblastine, and dacarbazine (AVD) with (n=18) or without (n=2) bleomycin. In all 20 patients, the final prescribed dose was 30.6 Gy in 17 fractions with IMRT. Four patients (20%) were treated with S-ISRT, 8 (40%) were treated with RD-ISRT (with doses of 19.8–25.2 Gy to the CPLNs), and 8 (40%) received M-ISRT (excluding the CPLNs entirely). A CPLN soft tissue

remnant was identified after chemotherapy in 11 patient (3 of 4 patients subsequently treated with S-ISRT, 4 of 8 with RD-ISRT, and 4 of 8 with M-ISRT).

At a median follow-up time of 4 years (range 0–9 years) from diagnosis to last follow-up, the 4-year PFS rate was 94.7% for the 20 patients with CPLN involvement who achieved a complete response to ABVD and received consolidative RT (Figure 1). All patients were alive at last follow-up. Only one patient experienced relapse. This patient presented with stage IIB HL at age 22 with bilateral neck, axillary, and bulky mediastinal involvement (Figure 2), with a 5.8-cm CPLN that was distinct from the site of bulky mediastinal involvement. After completion of 6 cycles of ABVD, post-chemotherapy PET-CT revealed a CR, with a residual CPLN remnant of 2.7 cm. The patient was treated with a reduced dose of 21.6 Gy to the CPLN site and full dose of 30.6 Gy to other sites of initial involvement (i.e., RD-ISRT). The relapse occurred both within the RT field (upper mediastinum) and outside the RT field (right lung, biopsy proven) but not in the CPLN region. That patient received salvage chemotherapy and autologous stem cell transplantation and was alive in CR at the time of last follow-up.

Median doses to OARs in each of the three subgroups are listed in Table 2. On analysis, several dosimetric variables, primarily related to cardiac dose, appeared lower in the M-ISRT group. The volume of heart that received 25 Gy (total heart V25) was higher for the S-ISRT group (41.0%) than for the RD-ISRT group (29.4%, $P=0.078$ or the M-ISRT group (25.8%, $P=0.025$). The mean heart dose was significantly lower for patients treated with M-ISRT compared to S-ISRT ($P=0.043$). Other mean doses were not statistically different between subgroups, however there were trends towards lower OAR doses on the RD-ISRT and M-ISRT groups that could be clinically meaningful. For instance, the volume of the right breast that received 25 Gy (right breast V25) was 5.5% in the S-ISRT cohort compared to 2.6% in the RD-ISRT group ($P=0.170$) and 1.3% in the M-ISRT ($P=0.055$).

Finally, to assess the extent of normal tissue sparing accomplished by M-ISRT, we produced a second set of S-ISRT plans (which included the involved CPLN site) for the 8 patients who had received M-ISRT (Figure 3). Including the CPLN site in the target volume significantly increased the doses to the total heart, LV, and coronary arteries (Table 3). The mean heart dose for those 8 patients increased from 11.8 Gy to 14.4 Gy ($P=0.008$), and the volume of the heart that received 5 Gy (heart V5) increased from 49.6% to 65.1% ($P=0.003$), but the differences in the mean lung dose, lung V20, and lung V5 were not clinically significant. Among the 6 female patients in the M-ISRT group, re-planning with S-ISRT significantly increased the left breast V5 (14.3% vs. 6.3%, $P=0.005$).

DISCUSSION

The overarching goal in the management of early-stage HL is to maintain excellent rates of cure while minimizing long-term treatment-related toxicity, most notably cardiac and pulmonary morbidity and secondary malignancies. Historically, extensive RT fields, higher radiation doses, and alkylating chemotherapy were largely responsible for severe adverse effects among aging HL survivors [2]. Therapeutic de-escalation has been explored by limiting the number of chemotherapy cycles, omitting systemic agents (e.g., bleomycin),

reducing RT field size, limiting RT doses, and even omitting RT altogether [4,17–19]. The ultimate challenge is accurately identifying which patients can benefit from treatment de-escalation without compromising cure.

In the current study, we examined outcomes among patients who received combined-modality therapy for HL and known CPLN involvement. In a similar study, 11 of 153 patients with HL (7%) had CPLNs detected on CT scans at diagnosis or during follow-up [9]. The higher rate of involvement in our study (17%) may reflect our routine use of PET-CT rather than CT scans for disease staging. On CT scans, the size of CPLNs that indicates pathologic involvement is controversial, with proposed cutoffs of 5 mm, 8 mm, and 10 mm [20–22]. PET-CT is more sensitive for detecting involved CPLNs. One retrospective review of 1,200 PET-CT scans obtained from cancer patients over a 20-month period revealed that 9 patients had FDG-avid CPLNs, but only 3 of those 9 had evidence of CPLN involvement on CT scanning [23]. Because our patients were all referred for consolidative RT for HL, stage II disease and bulky involvement were common, which also could account for the higher rate of CPLN involvement.

After the widespread adoption of chemotherapy as the mainstay of HL treatment, radiation field sizes have decreased significantly, in large part because most relapses after chemotherapy alone for stage I or II disease occur at sites of initial disease [24]. Randomized trials have demonstrated equivalent efficacy for extended-field radiation therapy and involved-field radiation therapy after chemotherapy [18,25]. Involved-node radiation therapy (INRT), in which only involved nodes identified on pretreatment PET-CT are included in the consolidative radiation target, has been implemented at several centers and seems to be as effective as IFRT [26]. However, this approach requires that the pre-chemotherapy PET-CT scan be obtained while the patient is in the RT treatment position, which is not feasible at many centers. The ILROG proposed ISRT as a modification of INRT that would account for set-up differences by using slightly increased margins [1]. However, CPLN involvement is a concern even for patients undergoing ISRT because the CPLNs are located in the inferior thorax near the heart. Therefore disease involvement in this location has the potential to impact RT doses to the heart, lungs and, among female patients, the breasts.

In the current study of 20 patients with CPLN involvement who received consolidative RT after a complete response to ABVD, the RT was de-escalated in 16 patients, either through reduction of the prescribed dose to the CPLNs or exclusion of the CPLNs from the target volume. After a median observation time of more than 4 years, no patient who received M-ISRT had a relapse, and only 1 patient treated with RD-ISRT had a relapse, which was located in the initial site of bulky disease and in the parenchymal lung, but not in the CPLN region treated to 21.6 Gy.

Identifying patients with HL for whom consolidative RT can be omitted is the subject of much study. Indeed, one limitation of the current study, beyond its retrospective nature, lies in the variability of selection for treatment with standard, reduced dose or modified ISRT fields. There were not any striking differences in the patient age, number of cycles of ABVD administered nor proportion of female patients in each treatment group. However, in general

patients treated with M-ISRT fields tended to have smaller CPLNs at diagnosis as well as smaller nodal remnants visible after ABVD, likely reflecting the perceived lower risk of relapse in this area by the treating physician. In several large phase III trials, a negative interim PET-CR after 2–3 cycles of ABVD has been used to identify patients who could be treated with chemotherapy alone. The 2×2 EORTC/LYSA/FIL H10 was one such trial, designed to improve the choice of treatment intensity based on early evaluation of response with PET-CT after 2 cycles of ABVD; the non-inferiority of ABVD alone relative to ABVD with INRT could not be demonstrated among patients with stage I or II favorable HL or unfavorable HL [4]. In an intent-to-treat analysis of the subgroup with favorable disease, the 5-year PFS rate was 99% in the ABVD+INRT arm versus 87.1% in the ABVD-only arm (HR 15.8, 95% CI 3.8–66.1). Similar findings were reported from the UK RAPID trial [5]. These studies highlight the inadequacy of negative early PET-CT to distinguish between patients who do and do not benefit from RT. In the current study, the interim PET scan after 2 chemotherapy cycles was negative (for the 12 patients who had that data available), but no such PET-CT scans were obtained in 8 patients (40%). On the other hand, evidence of disease on the interim PET scans, especially in the CPLN region, may be a deterrent to considering M-ISRT.

Despite the superior PFS among patients who received combined-modality therapy in published randomized studies, many oncologists are willing to omit RT and accept the increased risk of relapse in exchange for potentially lower risks of cardiac morbidity and secondary malignancy. Possibly some radiation oncologists adopt this strategy when designing consolidative RT fields, giving some consideration to omitting limited areas of initial involved sites if the perceived toxicity from treatment exceeds the potential benefit with regard to local control and the omission will result in a significant reduction in OAR doses. In a survey of expert radiation oncologists addressing HL cases, variable interpretation of ISRT for CPLN was demonstrated, often reflecting concerns regarding toxicity [27]. In our study, 8 patients were treated with M-ISRT, where the site of CPLN involvement was excluded from the target volume out of concern for increased cardiac doses. A set of comparison plans for those 8 patients that included the CPLNs in the clinical target volume showed increases in both high and low doses to most cardiac structures as well as increased dose to the left breast. Numerous survivorship studies have demonstrated an association between doses to OARs and long-term treatment-related morbidity and mortality. A recent nested case-control study of 2,617 5-year HL survivors treated in the Netherlands in 1965–1995 identified a strong correlation between mean heart dose and risk of coronary heart disease [28]. This relationship was linear, with an excess relative risk of 7.4% per 1 Gy increase in mean heart dose. Studies of long-term HL survivors suggest that careful attention to normal-tissue doses is essential for such patients.

Correlations have also been noted between relapse after chemotherapy alone and residual PET-negative masses on CT. One retrospective analysis of 105 patients with negative PET scans after chemotherapy for HL revealed that the size of the residual mass on CT was associated with inferior disease-free survival: the 5-year disease-free survival rate was 82% for patients with masses <4 cm and 50% for patients with masses ≥4 cm ($P=0.029$) [29]. If M-ISRT is being contemplated, the size of the residual mass may influence this decision, as would the extent of volume reduction. In the current study, roughly half of patients had no

evidence of a nodal remnant after ABVD. Moreover, the involved CPLNs shrank substantially in the group of RD-ISRT and M-ISRT (85.1% for RD-ISRT and 82.7% for M-ISRT) relative to the decrease in the group of S-ISRT (50.8%). The number of cycles of systemic therapy is an additional important consideration, as lower doses of RT may be adequate when more than 4 cycles of ABVD are given for HL patients with early stage unfavorable disease [30]. In the current analysis, the median number of chemotherapy cycles for all patients was 6; omission of sites of initial involvement may be less desirable after limited systemic therapy.

The decision to omit an initially involved site from the radiation target volume must not be taken lightly because of the potential increase in risk of relapse. Although we did not detect any nodal failures in un-irradiated but previously involved CPLN sites, others have reported CPLN relapses. In one study of 37 patients given combined-modality therapy for stage I or II HL in 2009–2014, 6 patients did not have baseline pre-chemotherapy PET-CT to guide consolidative RT field design [31]. Among those 6 patients, 3 had recurrences in nodal regions immediately adjacent to the RT field, including 1 patient who had a failure in a right CPLN that in retrospect had been present on the baseline CT images. Moreover, although involved CPLNs are typically not bulky, patterns of failure in chemotherapy-only arms of prospective studies illustrate that patients with non-bulky disease are at risk of relapse in initial disease sites. In EORTC/LYSA/FIL H10, of 238 patients with early-stage favorable disease who received 4 cycles of ABVD alone, 30 experienced relapse, 22 (73%) exclusively in previously involved nodes, 5 (17%) in previously uninvolved nodes, and 3 (10%) in both. Fewer than 1% of patients in that trial had bulky disease, highlighting the benefit of consolidative RT even for patients without bulky disease. In the general population of patients with limited-stage HL, the lower likelihood of CPLN involvement makes it highly unlikely that any randomized trial will be conducted to identify patients for whom involved CPLN regions can be safely omitted. More nuanced evaluation of patterns of failure from prospective studies of patients treated with chemotherapy alone may help to guide the identification of patients who may be candidates for M-ISRT.

In this retrospective study of 20 patients who received consolidative RT after a CR to ABVD, reduced RT doses to the CPLN area or excluding the CPLNs from the RT field significantly reduced cardiac radiation exposure without any apparent increase in failure rates. Our findings are encouraging and provide some support for the selective omission of CPLN from the ISRT technique. However, these results must be considered tentative, given the small number of patients; only 8 had CPLNs entirely excluded from the RT fields. The decision to omit CPLN coverage requires an individual assessment of both the potential reduction in risk of toxicity and increase in risk of relapse, and should take into account factors such as the size of involved CPLNs before and after chemotherapy. Additional data from prospective trials are required before M-ISRT can be considered a standard approach.

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Fig. 1.

Progression-free survival for 20 patients with cardiophrenic lymph node involvement treated with ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) chemotherapy followed by consolidative radiation therapy.

Fig. 2.

22-year-old patient with stage IIB bulky Hodgkin lymphoma and cardiophrenic lymph node (CPLN) involvement treated with reduced dose involved site radiation therapy (RD-ISRT). A-C, baseline PET-CT scan before chemotherapy. D-F, intensity-modulated radiation therapy (IMRT) treatment plan, with deep-inspiration breath hold and the CPLN site treated to a dose of 21.6 Gy and the remaining field to 30.6 Gy. G-H, Sites of relapsed disease at 3 months after RT in the right lung and mediastinum. I, The site of the CPLN that received 21.6 Gy (annotated) was not a site of relapse.

Fig. 3.

Comparison plans in a patient treated with modified involved-site radiation therapy (M-ISRT). A-B, baseline PET-CT scan before chemotherapy. C, baseline contrast-enhanced CT scan before chemotherapy, with cardiophrenic lymph nodes (CPLNs) annotated. D, post-chemotherapy contrast CT scan shows residual CPLN remnant. E-F, the M-ISRT plan administered with the CPLN region omitted. G-H, comparison plan with the CPLN region included. The mean heart dose increased from 7.7 Gy to 11.7 Gy with standard ISRT.

Table 1.

Patient characteristics

	All Patients [n=169]	Patients with CPLN involvement [n=29]	Patients without CPLN involvement [n=140]	P Value
Age, median(range) years	30 (18.5–77.5)	27.1 (18.5–45.4)	30.8 (18.5–77.5)	0.44
Women, no. (%)	104 (62)	20 (69)	84 (60)	0.41
Ann Arbor disease stage, no. (%)				
I	11 (7)	0 (0)	11 (8)	0.48
II	141 (83)	26 (90)	115 (82)	
III	12 (7)	2 (7)	10 (7)	
IV	5 (3)	1 (3)	4 (3)	
B symptoms, no. (%)	74 (44)	16 (55)	58 (41)	0.22
Bulky mediastinal disease (>10 cm), no. (%)	70 (41)	16 (55)	54 (39)	0.15
No. chemo cycles, median (range)	6 (1–8.5)	6 (4–6)	6 (1–8.5)	0.97
RT for refractory disease, no. (%)	33 (20)	9 (31)	24 (17)	0.12
No. of CPLN, median (range)		1 (1–8)		
Size of largest CPLN, cm (range)		2.2 (0.9–10.1)		

Abbreviation: CPLN, cardiophrenic lymph node; RT, radiation therapy.

Table 2.

Characteristics of 20 patients with involved cardiophrenic lymph nodes who received consolidative radiation therapy for chemosensitive disease

Characteristic	Patients with CPLN treated to full dose (S-ISRT, n=4)	Patients with CPLN treated to lower dose (RD-ISRT, n=8)	<i>P</i> Value	Patients with CPLNs excluded from field (M-ISRT, n=8)	<i>P</i> Value
Female, no. (%)	3 (75)	5 (63)		6 (75)	
Median no. of CPLNs (range)	1	2 (1–4)		2 (1–3)	
Median node size at diagnosis, cm (range)	2.4 (1.1–4.1)	3.4 (1.4–9.1)		1.9 (0.9–3.6)	
Median prescribed dose to CPLN, Gy	30.6	21.6 (19.8–25.2)		-----	
Median no. of chemo cycles (range)	6 (4–6)	6 (6)		5 (4–6)	
4 cycles, no (%)	1 (25)	0		4 (50)	
6 cycles, no (%)	3 (75)	8 (100)		4 (50)	
Interim PET-2, no. (%)					
Positive	0 (0)	0		0	
Negative	3 (75)	4 (50)		5 (62.5)	
Not done	1 (25)	4 (50)		3 (37.5)	
Nodal remnant after ABVD, no. (%)					
Yes	3 (75)	4 (50)		4 (50)	
No	1 (25)	4 (50)		4 (50)	
Median size of nodal remnant, cm (range)	1.8 (0.6–2.2)	1.9 (1.1–5.6)		1.0 (0.5–1.6)	
Median reduction in CPLN size, % (range)	50.8 (1.5–100)	85.1 (38.5–100)		82.7% (45–100)	
Mean heart dose, Gy (SD)	16.6 (3.1)	14.9 (3.1)	0.381	11.8 (3.9)	0.060
Heart V25, % (SD)	41.0 (8.9)	29.4 (8.8)	0.056	25.8 (11.0)	0.038
Heart V5, % (SD)	67.0 (13.4)	66.8 (13.9)	0.977	49.6 (16.2)	0.096
Mean left ventricle dose, Gy (SD)	6.9 (3.5)	7.2 (3.0)	0.851	4.4 (2.3)	0.167
Left ventricle V25, % (SD)	8.3 (7.7)	5.4 (5.4)	0.467	3.3 (4.9)	0.195
Left ventricle V5, % (SD)	36.8 (23.7)	40.9 (19.6)	0.754	22 (14.3)	0.202
Mean dose to left main/LAD, Gy (SD)	16.7 (7.0)	16.9 (6.7)	0.974	12.8 (4.8)	0.283
Left main/LAD V25, % (SD)	44.3 (23.1)	43 (29.8)	0.943	27.3 (17.7)	0.184
Left main/LAD V5, % (SD)	58.5 (19)	64.8 (21.7)	0.636	51.1 (17.4)	0.516
Mean dose to right coronary, Gy (SD)	25.2 (8.4)	20.4 (5.9)	0.275	16.9 (9.8)	0.179
Mean right coronary V25, % (SD)	73.5 (30.04)	43.3 (25.2)	0.095	46.3 (35.6)	0.220
Right coronary V5, % (SD)	84.5 (23.7)	80.3 (25.5)	0.792	60.8 (29.7)	0.197
Mean lung dose, Gy (SD)	11.7 (1.6)	11.5 (1.9)	0.813	10.3 (1.4)	0.156
Lung V20, % (SD)	27.3 (5.3)	26.5 (6.7)	0.85	24.0 (3.5)	0.230
Lung V5, % (SD)	53.3 (7.5)	55 (7.0)	0.698	49.0 (7.8)	0.389
Mean dose to right breast, Gy (SD)	3.35 (0.5)	4.2 (3.0)	0.707	1.9 (1.1)	0.133
Right breast V25, % (SD)	5.5 (3.5)	2.6 (2.9)	0.304	1.3 (1.2)	0.032
Right breast V5, % (SD)	17.5 (7)	23.6 (17.8)	0.667	10.3 (6.0)	0.162
Mean dose to left breast, Gy (SD)	1.3 (0.8)	5.1 (4.0)	0.262	1.5 (1.2)	0.792
Left breast V25, % (SD)	1 (0)	5 (7.5)	0.541	1.5 (2.1)	0.906
Left breast V5, % (SD)	5.5 (4.9)	25.8 (19.1)	0.218	6.3 (5.7)	0.861

Abbreviations: CPLN, cardiophrenic lymph nodes; S-ISRT, standard involved-field radiation therapy; RD, reduced dose; M, modified; PET, positron emission tomography; ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; SD, standard deviation; LAD, left anterior descending [artery].

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Table 3.

Doses to organs at risk for patients treated with S-ISRT versus M-ISRT

Characteristic	Patients treated with M-ISRT (n=8)	Re-planned with S-ISRT (n=8)	P Value
Mean heart dose, Gy (SD)	11.8 (3.9)	14.4 (3.6)	0.008
Heart V25, % (SD)	25.8 (11.0)	30.8 (12.2)	0.025
Heart V5, % (SD)	49.6 (16.2)	65.1 (15.8)	0.003
Mean dose to left ventricle, Gy (SD)	4.4 (2.3)	6.5 (2.4)	0.007
Left ventricle V25, % (SD)	3.3 (4.9)	4.4 (4.9)	0.026
Left ventricle V5 (SD)	22 (14.3)	39.4 (20.5)	0.027
Mean dose to left main/LAD, Gy (SD)	12.8 (4.8)	17.3 (3.7)	0.019
Left main/LAD V25, % (SD)	27.3 (17.7)	37.9 (16.5)	0.065
Left main/LAD V5, % (SD)	51.1 (17.4)	72.1 (15.0)	0.004
Mean dose to right coronary, % (SD)	16.9 (9.8)	19.8 (8.8)	0.021
Right coronary V25, % (SD)	46.3 (35.6)	51.8 (37.8)	0.021
Right coronary V5, % (SD)	60.8 (29.7)	76 (19.5)	0.048
Mean lung dose, Gy (SD)	10.3 (1.4)	11.4 (2.0)	0.061
Lung V20, % (SD)	24.0 (3.5)	37.0 (5.8)	0.104
Lung V5, % (SD)	49 (7.8)	53.9 (11.7)	0.090
Mean dose to right breast, Gy (SD)	1.9 (1.1)	2.3 (1.0)	0.104
Right breast V25, % (SD)	1.3 (1.2)	1.8 (1.6)	0.08
Right breast V5, % (SD)	10.3 (6.0)	13.2 (5.4)	0.081
Mean dose to left breast, Gy (SD)	1.6 (1.2)	3.0 (1.9)	0.11
Left breast V25, % (SD)	1.5 (2.06)	3.3 (3.5)	0.069
Left breast V5, % (SD)	6.3 (5.7)	14.3 (8.9)	0.005

Abbreviations: S-ISRT, standard involved-site radiation therapy; M-ISRT, modified involved-site radiation therapy; SD, standard deviation; LAD, left anterior descending [artery].